Coexistent childhood renovascular and cerebrovascular disease

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Defining and refining the phenotype of *PRRT2* mutations

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This commentary is on the original article by Silveira-Moriyama et al. on pages 327–334 of this issue.

Paroxysmal dyskinesias constitute a group of episode movement disorders that have been historically classified based on precipitant, duration, and family history. Careful description of phenotypes has shown that classification based on precipitant is the most powerful for predicting features and clinical course. The three major groups are: (1) kinesigenic – triggered by sudden movement; (2) exertional – triggered by sustained exertion; (3) non-kinesigenic – no discrete trigger but with attacks often following ingestion of ethanol or caffeine, or after sleep deprivation. All three forms can exist as primary disorders or may be secondary to specific brain lesions. The primary forms typically begin in childhood and are not associated with neurologic abnormalities between episodes. Several causative genes have been described, but the major gene responsible for paroxysmal kinesigenic dyskinesia (PKD) has been elusive until recently.[1]

Silveira-Moriyama et al.[2] describe the clinical features of children with PKD and *PRRT2* gene mutations. Since discovery of the association between *PRRT2* mutations and PKD, there has been substantial progress in further defining the phenotypic spectrum of these mutations. Mutations in the *PRRT2* gene may cause PKD, infantile convulsions, or familial hemiplegic migraine.[2–4] *PRRT2* mutations may also cause episodic ataxia[5] or febrile seizures.[6]

In addition to contributions toward better understanding of the disorder and its prognosis, the findings of Silviera-Moriyama et al.[2] raise important conceptual questions about the pathophysiology of paroxysmal disorders. Early reports of paroxysmal dyskinesias raised the question of whether they might be a form of epilepsy, yet surface electroencephalography is normal during attacks. By convention, seizures are viewed as cortical phenomena due to the paroxysmal discharge of neurons. However, it is reasonable to hypothesize that paroxysmal dyskinesias are due to paroxysmal discharge of subcortical neurons. Supporting this notion is the exquisite clinical response of PKD to low doses of anticonvulsant medications such as carbamazepine or phenytoin. Can some forms of hemiplegic migraine also result from paroxysmal neuronal discharge? Or can *PRRT2* mutations lead to paroxysmal of neuronal depression? Further study of neuronal function in the setting of *PRRT2* mutations is likely to shed light on the pathophysiology of many paroxysmal disorders including seizures, migraine, paroxysmal movement disorders, and paroxysmal ataxia.

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This commentary is on the original article by Willsher et al. on pages 335–340 of this issue.

In their retrospective case note and imaging review of 34 children, Willsher et al.[1] point to the importance and frequently neglected association of coexisting renovascular disease and steno-occlusive cerebrovascular problems such as moyamoya or other complex occlusive cerebrovascular disease (OCVD). The patients were retrospectively identified having been investigated with cerebral and renal digital subtraction catheter angiography. The majority (11/14) with OCVD and about 20% of children with moyamoya had a renal artery stenosis. Accompanying hypertension could be detected in 20 out of 34, although whether it

was of renal, cerebral, or combined origin cannot be defined.

Amlie-Lefond et al.[2] recently described in a large cohort of 525 patients of the International Pediatric Stroke Study different types and predictors of cerebral arteriopathy in children with arterial ischaemic stroke. An arteriopathy was identified on vascular imaging in over half of the patient group. Focal cerebral arteriopathy was the most common type, followed by moyamoya (20%), and among others two patients with fibromuscular dysplasia, and 12% with vasculitis. These different subgroups can have hypertension, whether this is conditional on cerebral hypoperfusion or in connection with a renovascular problem. For instance, many vasculitides can cause renovascular hypertension as well.[2] Thus patients with arterial ischaemic stroke and vasculopathies should be examined more carefully in general regarding systemic vascular involvement.

Willsher et al. categorized 14 out of 34 children with complex OCVD defined as stenosis or occlusion of more than one cerebral or cervical artery, not meeting the criteria for moyamoya. Apparently it was not possible to categorize them using the criteria proposed by Sébire et al.[3] However, it could be that the new classification system proposed by Bernard et al.[4] gives the opportunity to classify them as 'aortic/cervical arteriopathy' or 'multi-factorial'. Besides that, it considers whether children with arterial ischaemic stroke and concurrent renovascular involvement who do not fulfil the criteria for Takayasu arteritis or fibromuscular dysplasia should be classified separately.

The fact that accurate blood pressure measuring is frequently neglected in children is important. Although treatments have to be considered very cautiously (compensatory cerebral hypertension), there is a diagnostic impact. Compensatory hypertension might also be easy to follow as an important marker for beneficial effects of treatment approaches to the vascular problem.

The comparison to the study of Togao et al.[5] has to be viewed critically as the age group (2–48years for Togao et al.'s study) is different; but as the underlying moyamoya is a progressive problem it is important to point out that two of four patients with renal artery stenosis were of childhood age. Compared with the data of Willsher et al. this is a significantly lower percentage and poses the question of whether the likelihood of renal abnormalities is different in moyamoya syndrome and moyamoya disease. The paper by Willsher et al. underscores the importance of searching for hypertension and renovascular abnormalities in children with OCVD, but also in those with moymoya (despite being less frequent), although the group of described patients is heterogeneous and highly selected. On the other hand, the level of suspicion regarding cerebrovascular diseases in patients with renovascular hypertension or systemic vascular disorders as fibromuscular disease has to be high.

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Chronic childhood ataxia: the cause depends on how you look

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Progressive or chronic cerebellar ataxia is often a troubling diagnostic challenge both in adults and children. In patients with adult onset ataxias, both genetic and acquired diseases merit consideration once overt structural causes of ataxia are excluded by imaging. Such disorders have cerebellar deficits as a core feature, with added motor and sensory signs that may indicate specific etiologies. Genetic and immune testing often allows very specific diagnoses but a substantial number of cases remain not fully characterized. The heterogeneity of genetic causes of ataxia and phenotypic heterogeneity resulting from particular gene mutations lead to difficulties in choosing the right tests and their interpretation.